REMARKS

I. Status of the Claims

Claims 1 and 9 are amended.

Claims 16-37 are withdrawn.

Claim 2 and 6 are canceled.

Claims 1, 3- 5 and 7-15 are under prosecution.

Applicant thanks the Examiner for withdrawing all rejections based on the amendments and arguments made in the response mailed September 20, 2007.

II. Claim 1 is Amended

Claims 1, 3-5 and 7-15 were rejected under 35 U.S.C. 112 first paragraph. On page 3 of the Office Action the Examiner admits the passage used in support of the amendment "clearly teaches custom fabrication of polymer size for molecular analysis based on the molecular weight of the molecule" but that was not the claim amendment. She objected, however, to the amendment "having pore sizes that are specific to a biomolecule". A new amendment is offered.

Claim 9 is amended to correctly depend on the antecedent claim.

III. A Prima Facie Case of Obviousness is Not Established

A. Claims 1, 3-5, 7-15 were rejected as obvious over Chang (U.S. Patent No. 6,994,964) and Chromecek (Publication of Specification No. 1,188,736). The Examiner claims that Chang disclosed a method for making a microarray with a macroporous polymer substrate (citing col. 13, lines 11-18 and Examples 1-2), monomers (cols. 13-15), aliphatic alcohol (col. 15, lines 50-62), coating a surface with a substrate (col. 21, lines 25-26), adding biomolecules (Ex. 1-3), and controlling pore size (col. 12, lines 21-28).

The Examiner admits that Chang "is silent regarding the mono and polyfunctional monomers forming the polymerization mixture wherein the size of the macropores is provided by the volumes of porogenic solvent." (Office Action, page 5). However, she claims on page 5

that this is known in the art. "It was well known in the art at the time the claimed invention was made that porous size is controlled by the amount of aromatic alcohol in the polymerization mixture as taught by Chromocek" (citing page 2 lines 85-94 to page 3 lines 15-26 and 58-64.)

Chang and Chromecek would not be combined by those of skill in the art because Chang purported to be an improvement over "porous matrices" as taught by Chromecek.

The examiner does not see any difference between brush polymer structures and matrix/cross-linked gels, whereas, as argued in the response of September 20, 2007, Chang himself separates clearly the object/component of his invention from the present invention.

Chang himself distinguishes very clearly that his patent is about using polymer brushes not "a porous matrix or a cross-linked polymer gel" (just above "Summary of Invention"; column 1, lines 44-55):

> Substrates reported used in array synthesis consist of flat two-dimensional surfaces or three-dimensional surfaces such as a porous matrix or a cross-linked polymer gel. Although these substrates have been useful as the density of the array increased, signal to noise ratio under assay conditions decreased due to crowding, resulting often in decreased performance. These crowding and performance issues become more important as more applications for high density macromolecular arrays are being developed. Thus, there is a need for high density macromolecular arrays with good or improved performance under assay conditions. The present invention meets this need.

In other words, Chang clearly says here that his polymer brush IS NOT THE SAME as porous matrix or cross-linked polymer gel as in pending claims.

Chang's polymer brushers are e.g., "polynucleotides attached to a pHEMA glass substrate (Example 3). Those of skill in the art would not combine Chang with the art of "porous matrices as in the present claims, because Chang was to be an improvement over porous matrices. Present claims are to improve porous matrices used for microarrays.

The examiner cites to specific dependent claims, but all depend on claim 1 so removing rejections to claim 1 should resolve the dependent claim rejections also.

B. Claims 1, 3-5, 7-12, 14-15 were rejected as obvious over Nakashima (U.S. patent 4,352,884) and Hammen (U.S. publication 2002/0043499) and Chromecek (discussed in the previous paragraph.)

On page 8, the examiner on page 8 says that Nakashima disclosed a method for making a microarray with a macroporus polymer substrate. However, the Examiner admits that Nakashima is silent regarding the size of the macropores being provided or controlled by the volumes of porogenic solvent. The Examiner again states that it is known in the art that porous sizes controlled by the amount of aromatic alcohol in the polymerization mixture is taught by Chromecek.

Nakashima's patent does not disclose any method for making microarrays. Microarrays (called also chips or biochips) are miniaturized arrays of different biomolecules (oligonucleotides or cDNA or proteins) called probes used to analyze sequence of e.g., RNA/DNA targets of interest or protein targets of interest. An important feature of microarrays is small size and multiplexity of analysis, i.e. each assay includes many (from hundreds to hundred of thousands) interactions between probes and target(s). Nakashima's patent does not contain any definitions/features/data that suggest a patent about microarrays as the examiner believe. Incidentally, microarrays appeared only in the late 80's and the beginning of 90's. Information about microarrays is available elsewhere, e.g.:

http://www.gene-chips.com/GeneChips.html#Related%20Meetings
http://en.wikipedia.org/wiki/Microarrays
http://en.wikipedia.org/wiki/Protein_microarray
http://www.genomicglossaries.com/content/printpage.asp?REF=/content/instrument_tech.asp

Nakashima's patent is about methods of immobilization of biomolecules on different substates. This patent has nothing connected to microarrays. For all existing microarrays, some substrates and immobilization methods are used, but this does not mean that substrates for immobilization and immobilization methods are equivalent to microarrays.

A porogenic solvent is one which dissolves the monomer mixture being polymerized but which does not dissolve the polymer , i.e., it is thermodynamically good solvent for monomers but thrmodynamically poor solvent for the forming polymer, but not just some solvent containing alcohol as the examiner thinks referencing Example 1 in Nakashima's patent.

Nakashima does not speak anywhere in his patent about porogenic solvents, and there are

no evidence anywhere that 0.5% aqueous ethanol solution is a porogenic solvent for monomers from Example 1.

In the pending application, there are references to articles describing porogenbic solvents:

> [0233] Horak, D et al., (1993) The Effect of Polymeric Porogen on the Properties of Macroporous Poly(Glycidyl Methacrylate-co-Ethylene Dimethacrylate). Polymer 34, 3481-3489.
> [0236] Svec et al., (1995) Kinetic Control of Pore Formation in macroporous Polymers. Formation of "Molded" Porous Materials with High Flow Characteristics for Separations or Catalysis. Chem. Mater. 7, 707-715.

Porogenic solvent is also defined in the present application at least at the following location:

> [0027] thermodynamically a poor solvent--a solvent that contributes to pore formation during polymerization. Solubility is good for initial monomers but poor for forming polymer--this phenomenon results in the precipitation of forming polymer particles. Porogenic solvent could be a mix of cyclohexanol, different aliphatic alcohols and may contain aromatic alkyl derivatives (e.g., toluene, xylene).

In addition, Chromecek patent also describes.

First page, lines 9-13: It is well-known that copolymerization of styrene with divinyl benzene in the presence of liquids dissolving said monomers, but unable to dissolve the copolymer results in macroporous copolymers (copolymers with apparent porosities).

A microarray cannot be a microarray without immobilization of many probes.

The examiner stated:

> it was a well known in the art at the time of the invention that porous size are controlled by the amount of aromatic alcohol in the polymerization mixture...

Office Action, page 5.

The examiner still does not appear to distinguish polymer composition/properties and properties of material onto which the polymer is applied. In Nakashima's patent the term "macroporous" is used to characterize the material onto which polymer is applied (or polymer covers this material), see column 2; lines 47-68:

> The substrate or base material to be coated with the above copolymer can be one of various materials which is selected according to the intended application but generally speaking, includes inorganic materials such as glass, activated carbon, silica, alumina, and the like, synthetic high polymers such as polystyrene, polyethylene, polyvinyl chloride, nylon, polyester, polymethyl methacrylate, and the like, and naturally occurring high polymers such as cellulose.
>
> These materials are suitably employed in the form of grains, webs, sheets, tubes, electrodes, and the like. Such base materials are desirably used selectively in accordance with the intended applications. For example, when the intended application is a clinical selective adsorbent, the base material is preferably in the form of grains with a particle diameter of 0.05 to 5 millimeters. Glass beads are most desirable in that they are free from the problem of a portion being destroyed by friction in use and fragments thereof finding their way into the blood or being dissolved in the blood and transmitted into the body.

Col. 2, lines 47-68:

> When the intended application is an adsorbent for affinity chromatography or a column for chromatographic analysis, the base material is preferably in the form of grains or a tube of glass or synthetic resin. When the base material is an electrode, the carrier can be used for a quantitative determination of specific substances through reactions involving bio-active materials such as antigens, antibodies, complements, enzymes, and the like. Further, as a particulate base material, a porous material having a large surface area is preferred because it will immobilize a large amount of bio-active material per unit weight.

Col. 3; lines 5-12:

In other words, there are no teachings about porosity of the polymer which Nakashima produces; he only says that it is possible to apply his polymer onto some ready-to-be-used porous base.

The inventor is prepared to declare that 0.5% aqueous ethanol solution (Example 1-2 of Nakashima) IN NO WAY could be treated as porogenic solvent, and IT IS NOT porogenic for

this system; Nakashima himself does not speak anywhere about porogenic solvents or pore formation during polymerization of his polymer compositions. One of skill in the art would not be taught macroporous polymer substrates useful for microarray for immobilization of biomolecules.

There is no evidence that provides by the examiner that "Nakashima et al disclose a method of making a microarray with a macroporous polymer substrate..." as the examiner states. Moreover, on the next page, the examiner states the opposite: "Nakashima et al further teach... but they are silent regarding immobilizing to form a microarray." These are contradictory statements.

The examiner added Hamman for teaching immobilized biomolecules. Hammen does not relate anything that would lead one of skill in the art to form macroporous polymeric using parogenic solvents to form microarrays with large biomolecule cites from Hamman do not relate to the present invention. Hamman relates synthetics of molecules.

The examiner cites:

> [0074] The above described matrix can be deployed in a variety of chemistry formats, depending upon the nature of the chemical modifications of the IPN. In this regard the composites can be used for solid supported chemical synthesis operations. Synthesis procedures can be employed for synthesis of oligonucleotides, peptides, combinatorial chemistry libraries, and other substances that are adaptable to solid supported synthesis arrays. Such solid supported synthesis composites can be used in a series or more preferably in a parallel fashion. Preferred embodiments of parallel synthesis composites include microtiter plates equipped with a porous glass fiber frit in the bottom of the wells of the microtiter plates. Preferred porosities for the frits are from 1-20 microns. The interstitial volumes in the pores of the frits can be modified with an IPN that is chemically modified so as to provide an appropriate reactive group for initiating solid phase chemical synthesis procedures. A more preferred embodiment of the microtiter plate format of the composites of the present invention will make use of small quantities, varying from 10-100 milligrams, of nonporous beads, that are preferably 540 microns in diameter, in a microtiter plate, thus making a parallel series of minicolumns after the IPN matrix has been synthesized by the methods of the invention. A most preferred embodiment of the parallel synthesis composites is a matrix of glass fibers (filter paper) with preferred pore diameters

> of 5-40 microns, that has been bound with an IPN that is suitably substituted with moieties useful for initiating solid phase synthesis procedures. A planar array made with porous filter paper and substituted with a IPN in the solid matrix can be used for massively parallel operations that are limited only by the spot size of the array synthesis instrument device.

Hammen does not discuss anywhere formation of porous polymer with use of porogenic solvents.

In summary, a prima facie case of obviousness has not been established.

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR, 127 S.Ct. at 1740-41 (emphasis added). "[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art." *Id.* at 1741.

IV. Conclusion

If there are any remaining issues, the applicants' representative requests an interview prior to issuing an Office Action.

Applicants request allowance of the pending claims. No fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21416-93965).

Respectfully submitted,

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